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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/009,945	06/21/2002	Gerald H Thomsen	10624-092	8725

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EXAMINER	
ROBINSON, HOPE A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 06/01/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/009,945	THOMSEN ET AL.	
	Examiner	Art Unit	
	Hope A. Robinson	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 March 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *69-75,77,78 and 81-106* is/are pending in the application.

4a) Of the above claim(s) *73 and 74* is/are withdrawn from consideration.

5)☒ Claim(s) *78,81,82 and 85-87* is/are allowed.

6)☒ Claim(s) *69-72,75,77,83,84 and 88-106* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's response to the Office Action mailed October 6, 2004 on March 7, 2005, is acknowledged.

2. Claims 1-68, 76 and 79-80 have been canceled. Claims 69, 71 and 77-78 have been amended. Claims 81-106 have been added. Claims 69-75, 77-78 and 81-106 are pending. Claims 69-72, 75, 77-78 and 81-106 are under examination.

3. This application contains claims 73-74 drawn to an invention nonelected with traverse July 1, 2004. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

4. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

5. The following grounds of objection/rejection are or remain applicable:

Specification

6. The specification is objected to because of the following informalities:

(a) The specification remains objected to because trademarks are disclosed throughout the instant specification and not all of them are capitalized or accompanied

by the generic terminology. The use of the trademarks such as TRITON-X-100, for example, have been noted in this application (see page 47). It should be capitalized wherever it appears and be accompanied by the generic terminology. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner, which might adversely affect their validity as trademarks. It is noted that applicant made corrections of some trademarks, however, others remain. Applicant is advised to carefully check the entire specification.

Claim Rejections - 35 U.S.C. ɔ 112

7. Claims 69-72 and 77 are rejected under 35 U.S.C. 112, first paragraph, written description for the reasons of record.

Response to Applicant's Arguments:

8. The response on page 16 state that claims 76 and 79-80 have been cancelled, however, claim 69 has been amended to essentially recite all the limitations of the cancelled claim 76. Note that claim 69 is now rejected under 35 U.S.C. 112, first paragraph, written description for the reasons of record based on applicant's amendments to the claim. Applicant also state that one skilled in the art could readily envision each and every species of the claimed genus based on its relative identity to a definite structural feature: SEQ ID NO:2. Applicant cites MPEP 2164, stating that 112, first paragraph has been interpreted to require that the claimed invention be enabled so that any person skilled in the art can make and use the invention without undue

experimentation (see page 17 of the response). This argument is not persuasive because the rejection is made under 35 U.S.C. 112, first paragraph, written description with concerns possession, not enablement. In addition, applicant has not demonstrated in the instant specification possession of the large amount of fragments encompassed in the claims or provide a representative number of species for the large genus contained in the claims. A skilled artisan cannot envision the detailed chemical structure of the claims because there is no description as to a conserved region or what composition of amino acids are present or absent in SEQ ID NO:2. Applicant states that the specification on page 24-27 provides guidance regarding derivatives (e.g. insertions, deletions, substitutions etc.). However, there is no guidance as to where in the structure the changes will occur or what the changes will be. Claim 69 for example does not recite a functional limitation *per se*, therefore, the function that will be monitored by the claimed method is not recited in the claim. The prior art recognizes that modifications affect the protein structure-function relationship and a non-functional protein can result with a single amino acid change. Therefore, for all these reasons and the reasons of record the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

9. Claims 69-72, 77 and 88-91 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time

the application was filed, had possession of the claimed invention. The claims recite added material, which is not supported by the original disclosure. Independent claim 69 recite "wherein the Smurf activity detected is the activity of a Smurf comprising greater than 80% identity with the amino acid sequence depicted in SEQ ID NO:2" and there is no support for this in the instant specification. On page 21 of the specification it is disclosed that "...two amino acid sequences are "substantially homologous" or substantially similar" when greater than 70% of the amino acids are identical, or greater than about 90% are similar (functionally similar)...". There is no disclosed Smurf having the activity of a Smurf with greater than 80% identity to SEQ ID NO:2.
It is suggested that applicant delete the above phrase in the claim. Therefore, the specification lacks adequate written description. Note that the rejection under 35 U.S.C. 102 has been withdrawn in view of the amendments to claim 69, however, the rejection will be reinstated once the new matter is removed.

10. Claims 92-106 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to a method of screening for a modulator of Smurf activity and the claims do not specify what Smurf protein is being monitored, for example, provide a reference structure. The instant specification on page 24 outlines wild type Smurf1 or Smurf2 (vertebrates) and the art recognizes Dsmurf (Drosophila),

thus without a reference point a skilled artisan would not be able to practice the claimed method as claimed. The instant application recognizes that Smurf1 and Smurf2 are structurally and functionally different (see page 13 of the specification). Thus, the claims lack adequate written description and does not demonstrate possession of the claimed invention. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. See *Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997)*. Therefore, a biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence. For example, even though a genetic code table would correlate a known amino acid sequence with a genus of coding nucleic acids, the same table cannot predict the native, naturally occurring nucleic acid sequence of a naturally occurring mRNA or its corresponding cDNA. *See MPEP 2163.*

Further, *Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir.1991)*, states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in *possession of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (See *Vas-*

Cath at page 1116). The skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. *See Fiers v. Revel, 25 USPQ2d 1601 at 1606 (CAFC 1993).*

Therefore, for all these reasons the specification lacks adequate written description, and one of skill in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed.

11. Claims 69-72, 77 and 88-91 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the proteins set forth in SEQ ID NOS: 2/4 and the disclosure in Beach et al. (WO 97/12962, April 10, 1997), does not reasonably provide enablement for any polypeptide fragment of SEQ ID NOS: 2/4. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The enablement requirement refers to the requirement that the specification describe how to make and how to use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement

and whether any necessary experimentation is undue. These factors include, but are not limited to: Quantity of Experimentation Necessary; Amount of direction or guidance presented; Presence or absence of working examples; Nature of the Invention; State of the prior art and Relative skill of those in the art; Predictability or unpredictability of the art and Breadth of the claims (see *In re Wands, 858 F.2d at 737, 8 USPQ2d at1404 (Fed. Cir. 1988)*. The factors most relevant to the instant invention are discussed below.

The amount of experimentation required to practice the claimed invention is undue as the claims encompass an unspecified amount of polypeptide fragments. The instant specification indicates that "Smurf proteins of the invention may contain at least about 5 and preferably at least about 10 contiguous amino acids from the sequences set forth in SEQ ID NOS: 2/4" (see page 4). Page 21 of the specification provides a definition of what is considered to be "substantially homologous/similar" and page 24 of the instant specification discloses that derivatives or analogs are encompassed that are functionally active, i.e. capable of exhibiting one or more functional activities associated with a full-length wild type Smurf. However, the instant specification does not demonstrate any fragments of the claimed sequence having a Smurf activity. It is noted that the prior art discloses ubiquitin ligases (E3) with a sequence that is 77% and 99% identical to the claimed sequences (SEQ ID NO:2 and 4, respectively), however, the disclosed reference does not enable a sequence that is 79%, 80%, 85% to for example SEQ ID NO:2. Additionally, there is no demonstration of such a sequence having the desired activity. The instant protein could be non-functional or have a different function, thus, a skilled artisan would not know what activity to monitor in the claimed method

absent guidance/direction. A large quantity of experimentation would be necessary to generate the infinite number of fragments recited in the claims and possibly screen same for activity and with the lack of guidance/direction provided in the instant specification, this is merely an invitation to the skilled artisan to use the current invention as a starting point for further experimentation. Thus, undue experimentation would be required for a skilled artisan to make and/or use the claimed invention commensurate in scope with the claims.

Predictability of which potential changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (for example, expectedly intolerant to modification), and detailed knowledge of the ways in which the protein's structure relates to its function. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, for example, multiple substitutions. In this case, the necessary guidance has not been provided in the specification. Therefore, while it is known in the art that many amino acid substitutions are possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited, as certain positions in the sequence are critical to the protein's structure/function relationship. It is also known in the art that a single nucleotide or amino acid change or mutation can destroy the function of the biomolecule in many cases. For example, various sites or regions directly involved in binding activity

and in providing the correct three-dimensional spatial orientation of binding and active sites can be affected (see Wells, Biochemistry, vol. 29, pages 8509-8517, 1990). The instant specification provides no guidance/direction as to which regions of the protein would be tolerant of modifications and which would not, and it provides no working examples of any variant sequence that is encompassed by the claims. It is in no way predictable that randomly selected mutations, such as deletions, substitutions, additions, etc., in the disclosed sequences would result in a protein having activity comparable to the one disclosed. As plural substitutions for example are introduced, their interactions with each other and their effects on the structure and function of the protein is unpredictable. The skilled artisan would recognize the high degree of unpredictability that all the fragments encompassed in the claims would retain the recited function.

The state of the prior art provides evidence for the high degree of unpredictability as stated above. Seffernick et al. (J. Bacteriology, vol. 183, pages 2405-2410, 2001) disclose two polypeptides having 98% sequence identity and 99% sequence identity, differing at only 9 out of 475 amino acids (page 2407, right column, middle and page 2408, Fig. 3). The polypeptides of Seffernick et al. are identical along relatively long stretches of their respective sequences (page 2408, Fig. 3), however, these polypeptides exhibit distinct functions. The modifications exemplified in the Seffernick et al. reference is small compared to those contemplated and encompassed by the claimed invention (see page 21 of the specification and claim 3, for example).

The specification lacks adequate guidance/direction to enable a skilled artisan to practice the claimed invention commensurate in scope with the claims. Furthermore, while recombinant and mutagenesis techniques are known in the art, it is not routine in the art to screen large numbers of mutated proteins where the expectation of obtaining similar activity is unpredictable based on the instant disclosure. The amino acid sequence of a protein determines its structural and functional properties, and predictability of what mutations can be tolerated in a protein's sequence and result in certain activity, which is very complex, and well outside the realm of routine experimentation, because accurate predictions of a protein's function from mere sequence data are limited, therefore, the general knowledge and skill in the art is not sufficient, thus the specification needs to provide an enabling disclosure.

The working examples provided do not rectify the missing information in the instant specification pertaining to the claimed variant. The nature and properties of this claim is difficult to ascertain from the examples provided as one of skill in the art would have to engage in undue experimentation to construct the variants of the claimed invention and examine the same for function.

The specification does not provide support for the broad scope of the claims, which encompass an unspecified amount of fragments. The claims broadly read on any fragment thereof for the given sequences (SEQ ID NO: 2/4). The issue in this case is the breath of the claims in light of the predictability of the art as determined by the number of working examples, the skill level artisan and the guidance presented in the instant specification and the prior art of record. This make and test position is

inconsistent with the decisions of *In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970)* where it is stated that "...scope of claims must bear a reasonable correlation to scope of enablement provided by the specification to persons of ordinary skill in the art...". Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue. See *In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404 (Fed. Cir. 1988).*

Thus, for all these reasons, the specification is not considered to be enabling for one skilled in the art to make and use the claimed invention as the amount of experimentation required is undue, due to the broad scope of the claims, the lack of guidance and working examples provided in the specification and the high degree of unpredictability as evidenced by the state of the prior art, attempting to construct and test variants of the claimed invention would constitute undue experimentation. Making and testing the infinite number of possible variants to find one that functions as described is undue experimentation. Therefore, applicants have not provided sufficient guidance to enable one of skill in the art to make and use the claimed invention in a manner that reasonably correlates with the scope of the claims, to be considered enabling.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

12. Claims 83-84 and 98-99 are rejected under 35 U.S.C. 112, second paragraph, as failing to set forth the subject matter, which applicant (s) regard as their invention.

Claims 83-84 and 98-99 are indefinite for the recitation of "interaction" as the claim do not set forth what the specific "interaction" is or what "interaction" is being inhibited. The word "interaction" means dealings, interface, contact, relations or communications. Claim 83 for example recites "Smurf activity is interaction of a Smurf WW domain with a PPXY domain" and it is unclear what the specific activity is, how are the two domains interacting, is it binding activity/interaction, for example?.

Conclusion

13. Claims 78, 81-82 and 85-87 are free of the prior art.

14. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP ɔ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of

the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Hope A. Robinson whose telephone number is 571-272-0957. The examiner can normally be reached on Monday-Friday.
If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Hope Robinson, MS

Patent Examiner 5/16/05

JON WEBER
SUPERVISORY PATENT EXAMINER